Faxitron radiographs of both knees were obtained and knees were harvested and sectioned through the joint for histologic analysis. Joints were scored using a semi-quantitative scoring system by scorers blinded to group designation, with results expressed as both summed and maximal scores.
Results: Pharmacokinetic analysis demonstrated good systemic exposure of compound in MPI-369 treated animals. There were no compound-related adverse-effects. Histologic scoring revealed severe OA in the majority of STR/ort mice, with considerable variability in all groups. Radiographic osteophyte size correlated with the histologic severity. Male mice had significantly more advanced OA than female mice ($p = 0.008$, 2-tailed T-test). Long-term (10 + months) treatment of mice with a potent broad-spectrum MMP-inhibitor did not affect severity of OA in this model. When the left and right knee OA scores were compared in 20 male mice, no correlation of either summed or maximal scores was observed.
Conclusions: In this study, long-term treatment with a potent broad-spectrum MMP-inhibitor did not affect progression of osteoarthritis. This finding contrasts to results published by Brewster et al. which described protection against progression of osteoarthritis in the STR/ort mouse after treatment with an inhibitor of MMP-1, -8, and -13. We observed higher levels of OA in males than in females, in agreement with the majority of the literature. Correlation of OA severity between left and right knees in the same STR/ort mouse has not been previously reported, but would be predicted to be similar as a result of identical predisposing factors in the same animal. The lack of correlation between knees in the same animal in this study indicates that factors beyond genetics, circulating factors and weight are important in OA progression and highlight the huge variability in this model. Due to the large variability and lack of response to long-term therapy with a broad-spectrum MMP-inhibitor, we do not recommend use of the STR/ort model for disease modification studies.

79 OUTCOME OF MICROFRACTURE IN CHONDRAL DEFECTS IS MODULATED BY ANATOMIC SITE IN GOATS

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Purpose: Determine the effect of anatomic site on cartilage and bone response to microfracture in a caprine model.
Methods: Chondral defects (4.5 mm diameter) were created unilaterally in the medial femoral condyle and lateral patellar groove of eight adult goats. Tubular chisels were used to score the cartilage, and a curette was used to remove the articular and calcified cartilages. An awl (0.5 mm diameter micro bur) and hammer were used to create three holes in the subchondral bone. Perforations were made uniformly within the defect sites at an approximate depth of 2–3 mm, and bleeding from the holes and filling of the defect was observed in all animals. The animals were splinted for 2 weeks. The animals were sacrificed at 3 months and the defects were scored grossly [ICRS Cartilage Injury Evaluation Package] and histologically. Analysis of the bone was performed using microCT. Data were analyzed using ANOVA.
Results: After three months, the defects were filled with tissue (Figures 1A and 1D). The gross appearance of the microfracture-treated defects in the groove was significantly better than those in the condyle ($p = 0.004$, Figure 2). The microfracture-treated defects in the groove were flush with adjacent cartilage and relatively smooth in appearance (Figure 1A). However, the microfractured-defects in the condyle were depressed in the center and showed evidence of fibrillation around the edges (Figure 1D). The tissues stained well with SafO, indicating cartilage formation (Figures 1B and 1E). The effect of site on histological scores did not reach the level of significance (based on analysis using ANOVA). The collapse or resorption of the subchondral bone under the defect was more prevalent in the condyle than the groove, as evidenced by the microCT images (Figure 1C and 1F). Additionally, there were indications of changes in the structure of the bone in both locations, with the density and morphology of the bone under the defect changing when compared to normal bone.
Conclusions: To the authors' knowledge, this study is the first to document the results of microfracture in a caprine model of chondral repair. It is also the first to demonstrate the importance of anatomical site on cartilage repair in this model. These results demonstrate cartilage restoration and relatively intact subchondral bone in the lateral groove of the goats, while bone collapse and/or resorption were observed in the femoral condyle. The differences due to site may be related to mechanical loading, differences in the thickness of the calcified cartilage and differences in the structure of the subchondral bone. The changes in the subchondral bone observed in both locations are consistent with those that have been described after the creation of chondral defects in goats, so this phenomenon may be due to the creation of the defects and removal of the articular and calcified cartilage, not the creation of microchannels. The appropriate surgical technique to be used when doing microfracture on goats should be investigated further. Additionally, the effect of anatomical site on cartilage repair has not been extensively documented and needs to be further evaluated to better understand its importance in large animal pre-clinical models and how it may correlate with clinical outcomes in humans. The overall results of this study suggest the caprine microfracture model discussed may be appropriate in cartilage repair evaluations where microfracture is used as control or microfracture enhancements are tested.

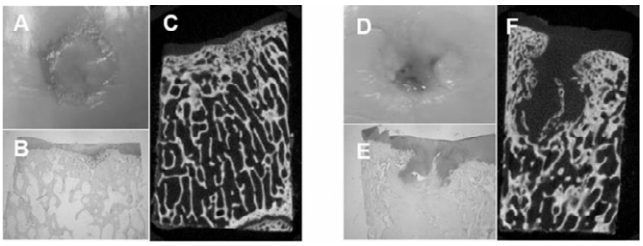

Figure 1. Representative images of the micro fractured defects in the lateral trochlear groove (A–C) and medial femoral condyle (D–F) at 3 months. Gross images (A,D) SafO-stained sections at 10× (B,E) and microCT images (C,F) are shown.

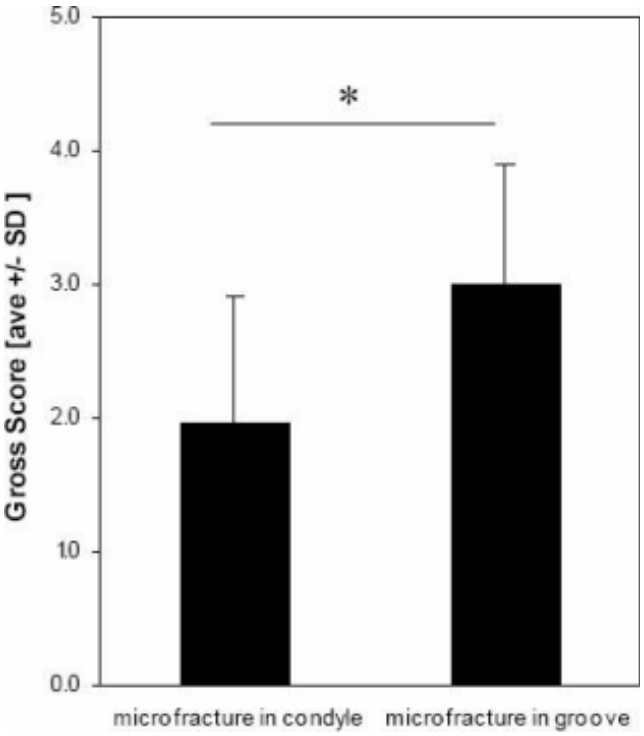

Figure 2. Gross scores for the microfracture-treated defects were significant higher in the groove than the condyle ($p = 0.004$). Data shown as average ±SD and all anatomic sites combined ($n = 8$).

80 A RABBIT KNEE MODEL OF CONTROLLED INSTABILITY

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Purpose: Joint instability associated with an ACL injury is a well-recognized risk factor that leads to post-traumatic OA in the human knee. Therefore, ACL transection (ACL-T) has been employed in several animal models to investigate post-traumatic OA. In ACL-T rabbit models, advanced OA (characterized by deep fibrillation and/or eburnation) predictably develops within 8 weeks of transection. Unfortunately, the severity

and rapidity of OA that develops in the rabbit ACL-T model is not optimal for piloting pharma-therapeutic treatments, or for investigating interaction of instability with other pathogenic factors. The goal of this study was to develop a rabbit model of controlled knee instability in which OA develops reproducibly at a level amenable to therapeutic interventions. The hypothesis was that, by inducing a more moderate level of instability in rabbit knees with a partial (rather than full) ACL-T, a reproducible, sub-critical level cartilage degeneration would occur.

Methods: With institutional approval, twenty-three New Zealand White rabbits received either total ACL-T (n = 8), partial (medial half) ACL-T (n = 8), or sham surgery (control, n = 7) on their left knees. Eight weeks later, the animals were subjected to a loading test, in which A-P stability of the knee was quantified in terms of anterior drawer stiffness and neutral-zone length. The joints were then prepared for histo-morphological evaluation. Femoral and tibial surfaces in both medial and lateral compartments were rated individually by Mankin score (each 14 points max), and the sum of these four scores was defined as the whole-joint score (56 points max).

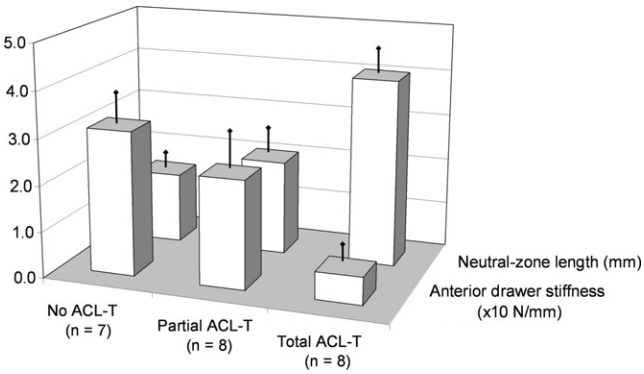

Figure 1. Results of Joint Laxity Tests.

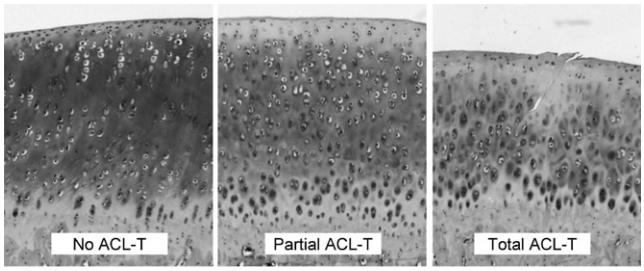

Figure 2. Cartilage histology of the medial femoral condyle (Safranin-O stained).

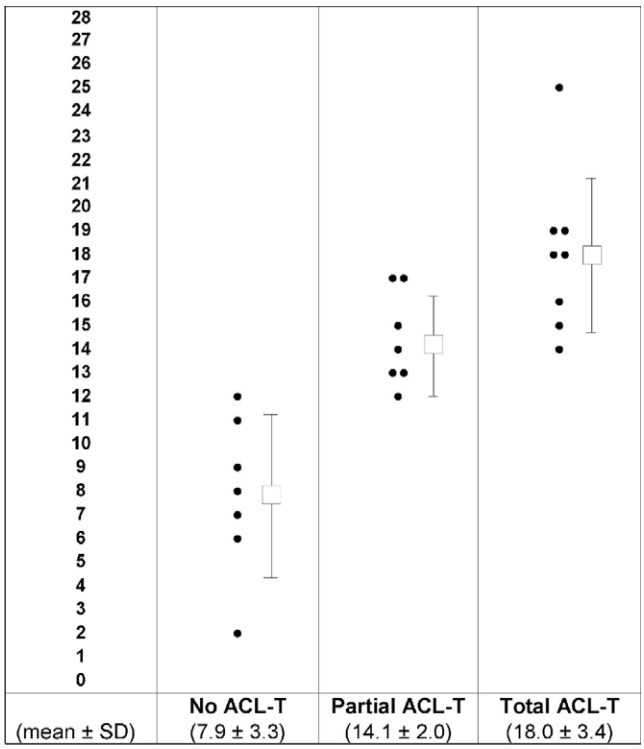

Figure 3. Whole-joint Mankin Score (56 points max.).

Results: A-P stability in the partial ACL-T knees was impaired with respect to the control knees, as evidenced by decrease of anterior drawer stiffness and increase of neutral zone length (Figure 1). However, the level of impairment was smaller than in the total ACL-T knees. Whole-joint Mankin scores in the partial ACL-T knees averaged 14.0±2.0 points (Figures 2 and 3); this was higher than in the control knees (7.9±3.3 points), but lower than in the total ACL-T knees (18.0±3.4) (P-values <0.05 for all cases).

Conclusions: Partial ACL-T created modest instability in rabbit knees. The cartilage degeneration that occurred in those knees at 8 weeks was at a sub-critical level. This rabbit knee model of controlled instability appears to be a promising tool for future OA research, especially for studies of multiple interacting influences.

81 THE INFLUENCE OF SUBCHONDRAL BONE LOSS ON ARTICULAR CARTILAGE DEGENERATION IN AN EXPERIMENTAL MODEL OF OSTEOARTHRITIS IN RATS

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Purpose: Osteoarthritis (OA) and osteoporosis (OP) are the most prevalent skeletal diseases related to ageing, but the relationship between these two diseases remains unclear. The purpose of this study is to investigate the relationship between OA and OP. Especially, the influence of subchondral bone loss on articular cartilage degeneration was evaluated in an experimental model of OA with ovariectomized (OVX) rats.

Methods: Eighty rats were randomized into two groups, and OP was experimentally induced prior to OA in one group by bilateral ovariectomy and the other was intact. Three months later, OA was experimentally induced by medial meniscectomy (MNX) in the right knee of 24 rats in each group (Week 0). MNX rats were sacrificed at 1−3 weeks after the MNX (n = 8 rats/point), and control rats were sacrificed at 0 and 3 weeks in each group. Three-dimensional (3D) structural change of tibial subchondral bone was evaluated using micro-focused X-ray computed tomography (micro-CT), followed by histological scoring (e.g. Scoring with HE/TB staining sections). In this experiment, to minimize the influence of body weight, feeding is strictly controlled, and the body weights were almost equal in these two groups (OVX or intact).

Results: Body weights at week 0 were 339.5±8.6 g for OVX group and 332.7±15.0 g for intact group. In the micro-CT analysis, tibial subchondral bone volume fraction (BV/TV) was significantly (12−16%) decreased in the OVX rats at 0−3 weeks. In the histological scoring system, articular cartilage was graded as normal (score 0) at Week 0 in both intact and OVX groups. The score was increased between 1 and 3 week by the MNX in the both groups, and they were not different between OVX and intact groups. It was reported that subchondral bone remodeling (increased bone turnover and subchondral sclerosis) plays an important role in the pathogenesis of OA (Ref. Arthritis Rheum 2004;50:1193–1206), however, the degree of articular cartilage degeneration by MNX was not different between OVX and intact groups.

Conclusions: In this study, subchondral bone loss was attained by OVX, and body weights were matched between OVX and intact groups. Under these conditions, the degree of articular cartilage degeneration by MNX was not different between OVX and intact groups. Subchondral bone loss did not promote articular cartilage degeneration in this study.

82 LOCAL ENDOCANNABINOID ENHANCEMENT REDUCES NOCICEPTION IN NATURALLY-OCCURING OSTEOARTHRITIS OF GUINEA PIGS

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Purpose: Dunkin Hartley guinea pigs begin to show signs of osteoarthritis at about 3 month of age which becomes progressively worse with advancing age. A powerful method to directly assess joint nociception without psychosocial and affective aspects of pain is to record the electrophysiological activity of joint nociceptive nerves.